In this issue of Clinical Cancer Research, Choi and colleagues (1) examine the impact that histology and coding mutations have on the long-term outcome of 247 lung adenocarcinoma cases that were resected in Korea. Non–small cell lung cancer (NSCLC) is the most important cause of cancer mortality worldwide, and lung adenocarcinoma is the most common histologic variant of the disease. This study represents the first drops of what will surely be an ensuing downpour of genomic data derived from “real-life” clinical cohorts, and in this respect picks up where large-scale, disease-focused genomic projects initiated by The Cancer Genome Atlas (TCGA), the International Cancer Genome Consortium (ICGC), and several larger private collections of retrospectively collected tumors have left off.

The advent of next-generation sequencing technology has allowed us to sequence tumor and normal DNA quickly, accurately, and inexpensively. Improvements in nucleic acid isolation and library generation chemistry have allowed us to do so from clinical samples, capturing and resequencing all the coding exons in the human genome reproducibly in many centers across the world. Finally, algorithmic advances in automated mutation calling have made the data analysis practicable in many international centers of excellence. In other words, unbiased, large-scale tumor/normal resequencing can now be done in many places in the world. The question now is “When should it be done?,” both to address pressing clinical questions and to affect the management of individual patients. Discovery of new and important mutations can and does still happen, but in heavily resequenced private collections of retrospectively collected tumors have left off.

Through an unbiased examination of the coding sequences and copy-number profiles of 247 patients with lung adenocarcinoma, Choi and colleagues (1) bring DNA sequence and copy number into play as a potential decision-making aids in early, resected lung adenocarcinoma. They begin with a discovery cohort of 170 patients with resected lung adenocarcinoma, of whom 65% had stage IA disease. This sample set is especially valuable because the stage IA population is an especially heterogeneous one for whom adjuvant therapy is not routinely recommended (8). The authors detected 22 significantly mutated genes, some overlapping with those reported in other studies (9–11) with some expected and unexpected exceptions. First, because neither whole-genome sequencing nor RNAseq was performed, the investigators did not identify any fusion genes in ALK, RET, ROS1, or NTRK1. In addition, the incidence of some known drivers, such as those in KRAS, was surprisingly low (6%), possibly due to sample purity, insufficient depth of sequencing, or both. Despite maneuvers to increase sensitivity of mutation detection through fine-tuning mutation calling algorithms (12), many of these probably artifically low rates of mutation remained, despite the background (passenger)
mutation rate increasing. This experience reinforces the powerful effects that the high background mutation rate in lung adenocarcinoma has on mutational significance, a problem exacerbated by sequencing with lower-than-needed depth of coverage, especially across key genes such as KRAS.

After evaluating and addressing, to as large an extent as possible, these technical issues, the authors then tackled the clinical questions relevant to the patients whose tumors comprised their dataset. They focused on the stage IA patient population introduced above, correctly recognizing that the management of this heterogeneous group is especially challenging due to the high recurrence rate, coupled with a lack of established adjuvant therapy benefit in this population (8), leading to a decision-making paralysis in the treating physician. Their training set suggested that stage IA patients with defects in the RB pathway had a worse prognosis after resection than did those patients with the RB pathway intact (Fig. 1). The validation set of tumors confirmed both the directionality of the finding in resected lung adenocarcinoma and the stage IA specificity of it.

The RB1 gene product is a major convergence point for many G1–S cell-cycle decisions. Because the topology of the pathway is largely known, the authors evaluated the phosphoprotein (inactive) levels of RB1, and the protein levels of E2F1, cyclins D1 and E1, in an effort to construct an immunohistochemistry-based assay using this pathway. Those efforts confirmed that the major members of this pathway behave as expected at the protein level, if the mutation and copy-number status of RB1 itself is known, setting the stage for a focused interrogation using a few antibodies and a targeted sequencing panel in stage IA resected lung adenocarcinoma.

This work greatly advances our understanding of the mutational landscape of lung adenocarcinoma, especially in Asian patients, but more work remains. With respect to characterization, deeper sequencing might show us that Asian and North American patients with lung adenocarcinoma are more alike than different. Capturing the fusion status of this or similar cohorts might educate us as to whether just as we expect more EGFR mutations in Asian patients, should we likewise expect more fusion kinases as well. Finally, RNA analysis would tell us how overlapping or
independent the effects of RB loss are on the transcriptional prognostic profiles of lung adenocarcinoma. That said, this data-set is an important foundation upon which we all can build to focus therapy where it is most needed in patients with resected lung adenocarcinoma.

References

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Received December 3, 2014; accepted December 30, 2014; published OnlineFirst February 2, 2015.
RB and Prognosis in Resected Lung Adenocarcinoma

Eric A. Collisson


Updated version Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-14-2931

Cited articles This article cites 12 articles, 4 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/21/11/2418.full#ref-list-1

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.